Personal genomics in psychiatry— a personal view

Bertram Müller-Myhsok
SENSE TO ORDER DIET DRINK WITH DOUBLE MEGA CHEESEBURGER MEAL (WITH FRY UPGRADE)

TENDENCY TO DRIVE BELLIGERENTLY SLOWLY IN THE LEFT LANE & NOT USE TURN SIGNALS.

ABILITY TO FIND CELL-PHONE "OFF" BUTTON IN THEATER

DELUSIONS OF STOCK MARKET SAVVY

URGE TO PURCHASE A SPORT UTILITY VEHICLE, & THEN COMPLAIN ABOUT GAS PRICES.

WILLINGNESS TO DROP $3.75 ON A CUP OF COFFEE.

BELIEF THAT ALL BAGS ARE CARRY-ON BAGS.

PROPENSITY TO DISCUSS WEATHER.

THE HUMAN GENETIC CODE, DECRYPTED.
TAKE TWO GENES AND CALL ME IN THE MORNING.
THE GLASS IS HALF FULL.

THE GLASS IS HALF EMPTY.
Figure 1. Predicted Cumulative Freedom from Myocardial Infarction, Ischemic Stroke, or Death from Coronary Heart Disease, According to Genotype Score.
Symptoms (DSM-IV-TR)

- Affective: Feelings of guilt and sadness, lack of enjoyment or pleasure in familiar activities or company
- Behavioural: Passivity, lack of initiative
- Cognitive: Frequent negative thoughts, faulty attribution of blame, low self esteem, suicidal thoughts, irrational hopelessness, difficulties in concentration and inability to make decisions
- Somatic: Loss of energy, insomnia, or hypersomnia, weight loss/gain, diminished sex drive
Some epidemiology

- **Life time prevalence:**
  - Women – 10-25%
  - Men – 5-12%

- **Average age to have the first major depression episode:** Mid 20s

- **One episode:** 60 % of a second
- **Two or three episodes:** 70-90 % have a following episode

- **One year after diagnosis:** 40 % are free of symptoms, 20 % have some symptoms, 40 % meet full criteria of the disorder
PERSPECTIVES

OPINION

How can we realize the promise of personalized antidepressant medicines?

Florian Holsboer
Outline

- Pharmacogenetics
  - Candidate gene study (ABCB1)
  - Adding effects linearly (genotypic scores)
  - Epistasis
  - Going beyond genetics

- Disease prediction
  - Gene x Environment interaction

- Desirables
PHARMACOGENETICS
Heterogeneous Antidepressant Treatment Response Pattern

HAM-D

Admission Week 1 Week 2 Week 3 Week 4 Week 5 Week 6 Week 7 Week 8
castle wall (barrier) function
Citalopram

1h after s.c. Injection of 1 µg citalopram / g bodyweight
Linkage disequilibrium (LD)
Cox-Regression Survival Analysis

non-substrates of P-glycoprotein

Wald value = 0.8; p = 0.38
Cox-Regression Survival Analysis

substrates of P-glycoprotein

Time [weeks]

non-remission [%]

C carrier (N=23)
non carrier (N=110)

Wald value = 13.3; p = 0.00027
Cox-Regression Survival Analysis

Wald value = 3.2; p = 0.073
Consequences

Therapeutic window

Genotype A
- No effect
- Effect
- Side effects

Genotype B
- Effect
- Side effects

Genotype C
- Effect
- Side effects

Dosage
Polymorphisms in the Drug Transporter Gene ABCB1 Predict Antidepressant Treatment Response in Depression

Manfred Uhr,1,# Alina Tontsch,1 Christian Namendorf,1 Stephan Ripke,1 Susanne Lucae,1 Marcus Ising,1 Tatjana Dose,1 Martin Ebinger,1 Marcus Roshenhagen,1 Martin Kohli,1 Stefan Kloiber,1 Daria Salyakina,1 Thomas Bettecken,1 Michael Specht,1 Benno Pütz,1 Elisabeth B. Binder,1 Bertram Müller-Myhsok,1 and Florian Holsboer1

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DOI 10.1016/j.neuron.2007.11.017
ADDING LINEAR EFFECTS
A Genomewide Association Study Points to Multiple Loci That Predict Antidepressant Drug Treatment Outcome in Depression

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Heterogeneous Antidepressant Treatment Response Pattern
Study design

- Two pharmacogenetic studies
  - MARS (Munich, n ~ 400)
  - STAR*D (USA, n ~ 1200)
- Genome-wide data
- Develop a genotypic score based on a linear combination of effects in MARS (GENOTYPIC RISK SCORES - GRS)
- Test this in STAR*D
Multi-Locus Analysis – STAR*D predicted from MARS

- Prediction model with non-genetic predictors and high vs. low number of response alleles: \( p = .025 \)

- Significant predictors:
  - Comorbid anxiety: \( p = .006 \)
  - No. of response alleles: \( OR = 1.28, p = .036 \)
EPISTASIS
Epistasis – basic idea
Genome-wide analysis of epistasis

- The problem:
  - SNP * SNP interactions
  - 500k data set
  - 124,999,750,000 possible 2-way interactions
  - $O(n^2)$
  - Computationally intense
Basic idea

• Use a simple statistic to approximate more standard analysis

• Calculate that statistic for all pairs as fast as possible

• Verify then by standard means
Approximation

\[ \sum_{i=\text{cases-only}} \left( \frac{\text{SNP } 1_i - \overline{\text{SNP } 1_i}}{n_i - 1} \right) \text{SNP } 2_i - \overline{\text{SNP } 2_i} \right) \left( \frac{\text{SNP } 1_i - \overline{\text{SNP } 1_i}}{n_i - 1} \right) \sigma_{\text{SNP } 1_i} \sigma_{\text{SNP } 2_i} - \sum_{j=\text{controls-only}} \left( \frac{\text{SNP } 1_j - \overline{\text{SNP } 1_j}}{n_j - 1} \right) \text{SNP } 2_j - \overline{\text{SNP } 2_j} \right) \left( \frac{\text{SNP } 1_j - \overline{\text{SNP } 1_j}}{n_j - 1} \right) \sigma_{\text{SNP } 1_j} \sigma_{\text{SNP } 2_j} \]
Speedup via GPU computing

• Graphics cards
  – Highly parallelized
  – Calculate approximation for 2000 x 2000 SNPs at a time
  – Time per approximation $1 \times 10^{-7}$ seconds
  – Speedup vs GPU around 1000
  – Use R, library GPUTOOLS
  – Wrapper for CUDA (NVIDIA)
  – Roughly one day per computer
EPIBLASTER-fast exhaustive two-locus epistasis detection strategy using graphical processing units

Tony Kam-Thong¹, Darina Czamara¹, Koji Tsuda²,³,⁴, Karsten Borgwardt⁵, Cathryn M Lewis⁶,⁷, Angelika Erhardt-Lehmann¹, Bernhard Hemmer⁸, Peter Rieckmann⁹, Markus Daake¹, Frank Weber¹, Christiane Wolf¹, Andreas Ziegler¹⁰, Benno Pütz¹, Florian Holsboer¹, Bernhard Schölkopf² and Bertram Müller-Myhsok*¹
Epistasis detection on quantitative phenotypes by exhaustive enumeration using GPUs

Tony Kam-Thong\textsuperscript{1,2,*}, Benno Pütz\textsuperscript{1}, Nazanin Karbalai\textsuperscript{1}, Bertram Müller-Myhsok\textsuperscript{1} and Karsten Borgwardt\textsuperscript{2}

\textsuperscript{1}Statistical Genetics, Max Planck Institute of Psychiatry, Munich and \textsuperscript{2}Machine Learning and Computational Biology Research Group, Max-Planck-Institutes, Tübingen, Germany

\begin{align*}
\text{epiHSIC}_{\text{empirical}}((X, Y), \mathcal{F}, \mathcal{G}) \propto & \\
& \alpha \left( \sum_{i} x_i^A x_i^B \psi(y_i) \right)^2 \quad (15) \\
& = \left( \sum_{i} x_i^A x_i^B \tilde{y}_i \right)^2 \quad (16)
\end{align*}
Heterogeneous Antidepressant Treatment Response Pattern

![Graph showing HAM-D scores over weeks from Admission to Week 8.]
Phenotype Distribution - % change after two weeks

mars$PCHANGE17ME_02WO

Frequency

-50 0 50 100

0 20 40 60 80

mars$PCHANGE17ME_02WO
Phenotype:

Drop in Hamilton ratings after two weeks of treatment

N = 511 patients genotyped over 536 750 SNPs (1.44*10^{12} SNP x SNP combinations)

<table>
<thead>
<tr>
<th>SNP1</th>
<th>SNP2</th>
<th>HSIC</th>
<th>Linear Regression</th>
<th>Interaction p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs11580794</td>
<td>rs11812623</td>
<td>7.70 \cdot 10^{-02}</td>
<td>4.42 \cdot 10^{-10}</td>
<td>0.9601</td>
</tr>
<tr>
<td>rs12910772</td>
<td>rs2338712</td>
<td>8.22 \cdot 10^{-02}</td>
<td>1.35 \cdot 10^{-10}</td>
<td>0.3682</td>
</tr>
<tr>
<td>rs13028359</td>
<td>rs2888542</td>
<td>8.24 \cdot 10^{-02}</td>
<td>7.39 \cdot 10^{-11}</td>
<td>0.2710</td>
</tr>
<tr>
<td>rs13401572</td>
<td>rs6130852</td>
<td>7.87 \cdot 10^{-02}</td>
<td>3.58 \cdot 10^{-10}</td>
<td>0.1360</td>
</tr>
<tr>
<td>rs2105126</td>
<td>rs1885418</td>
<td>7.90 \cdot 10^{-02}</td>
<td>2.62 \cdot 10^{-10}</td>
<td>0.2911</td>
</tr>
<tr>
<td>rs861256</td>
<td>rs11864516</td>
<td>7.93 \cdot 10^{-02}</td>
<td>1.78 \cdot 10^{-10}</td>
<td>0.4486</td>
</tr>
<tr>
<td>rs6442323</td>
<td>rs13186058</td>
<td>7.74 \cdot 10^{-02}</td>
<td>2.61 \cdot 10^{-10}</td>
<td>0.2621</td>
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<td>rs6442323</td>
<td>rs4958287</td>
<td>7.74 \cdot 10^{-02}</td>
<td>2.61 \cdot 10^{-10}</td>
<td>0.2621</td>
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<tr>
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<td>7.80 \cdot 10^{-02}</td>
<td>2.24 \cdot 10^{-10}</td>
<td>0.2621</td>
</tr>
<tr>
<td>rs7797027</td>
<td>rs1031912</td>
<td>7.87 \cdot 10^{-02}</td>
<td>2.72 \cdot 10^{-10}</td>
<td>0.7797</td>
</tr>
</tbody>
</table>
pair 2

I(as.factor(rs12910772_A):as.factor(rs2338712_A))

PCHANGE17ME_02WO

I(as.factor(rs12910772_A):as.factor(rs2338712_A))

PCHANGE17ME_02WO

l(as.factor(rs12910772_A):as.factor(rs2338712_A))
• **PBX1:**
  - pre-B-cell leukemia homeobox 1

• **MEIS2:**
  - Meis homeobox 2
  - *Meis 1 (RLS)*
  - P interaction between pair1 and pair2 = 0.0345
  - $r^2$ in both pairs around 8%
  - Area under ROC curve (AUC) = 0.58444
PBX and MEIS as Non-DNA-Binding Partners in Trimeric Complexes with HOX Proteins

KANDAVEL SHANMUGAM 1,2 NANCY C. GREEN 1 ISABEL RAMBaldi 1

Zebrafish Meis functions to stabilize Pbx proteins and regulate hindbrain patterning

Pbx/Meis Deficiencies Demonstrate Multigenetic Origins of Congenital Heart Disease

Kryn Stankunas,* Ching Shang,* Karen Y. Twu, Shih-Chu Kao, Nancy A. Jenkins, Neal G. Copeland, Mrinmoy Sanyal, Licia Selleri, Michael L. Cleary, Ching-Pin Chang

Abstract—Congenital heart diseases are traditionally considered to be multifactorial in pathogenesis resulting from environmental and genetic interactions that determine penetrance and expressivity within a genetically predisposed family. Recent evidence suggests that genetic contributions have been significantly underestimated. However, single gene defects occur only in a minority of cases, and multigenetic causes of congenital heart diseases have not been fully demonstrated. Here, we show that interactions between alleles of 3 Pbx genes, which encode homeodomain transcription factors, are sufficient to determine the phenotypic presentation of congenital heart diseases in mice. A major role is served by Pbx1, whose inactivation results in persistent truncus arteriosus. Reduction or absence of Pbx2 or Pbx3 leads to Pbx1 haploinsufficiency and specific malformations that resemble tetralogy of Fallot, overriding aorta with ventricular septal defect, and bicuspid aortic valves. Disruption of Meis1, which encodes a Pbx DNA-binding partner, results in cardiac anomalies that resemble those caused by Pbx mutations. Each of the observed cardiac defects represents developmental abnormalities affecting distinct stages of cardiac outflow tract development and corresponds to specific types of human congenital heart disease. Thus, varied deficiencies in the Pbx gene family produce a full spectrum of cardiac defects involving the outflow tract, providing a framework for determining multigenetic causes of congenital heart anomalies. (Circ Res. 2008;103:702-709.)
GOING BEYOND GENETICS
Not only genetics ....

- **GRS (Ising et al)**
  - **DexCRH data (MARS)**
    - Neuroendocrine marker
    - Response to CRH stimulation much higher in affecteds than in controls
  - **NMR data (Sämann et al)**
    - Certain areas in the brain have altered morphology (volumes) predicting response to treatment
Not only genetics ...

Area under ROC curve (AUC) = 0.745614
DISEASE PREDICTION
Polymorphisms in FKB5 are associated with increased recurrence of depressive episodes and rapid response to antidepressant treatment

Elisabeth B Binder¹, Daria Salyakina¹, Peter Lichtner², Gabriele M Wochnik¹, Marcus Ising¹, Benno Pütz¹, Sergi Papiol³, Shaun Seaman¹, Susanne Lucae¹, Martin A Kohli¹, Thomas Nickel¹, Heike E Künzel¹, Brigitte Fuchs¹, Matthias Majer¹, Andrea Pfennig¹, Nikola Kern¹, Jürgen Brunner¹, Sieglinde Modell¹, Thomas Baghai⁴, Tobias Deiml⁴, Peter Zill⁴, Brigitta Bondy⁴, Rainer Rupprecht⁴, Thomas Messer⁵, Oliver Köhnlein⁶, Heike Dabitz⁶, Tanja Brückl¹, Nina Müller¹, Hildegard Pfister¹, Roselind Lieb¹, Jakob C Mueller², Elin Löhmussaar², Tim M Strom², Thomas Bettecken², Thomas Meitinger², Manfred Uhr¹, Theo Rein¹, Florian Holsboer¹ & Bertram Muller-Myhsok¹
Patients with the TT genotype of rs1360780 respond faster to antidepressants.

![Graph showing HAM-D score over time for different rs1360780 genotypes (TT, CT, CC)].
FKBP5 and development of depression

Interaction of *FKBP5* Gene Variants and Adverse Life Events in Predicting Depression Onset: Results From a 10-Year Prospective Community Study

**Petra Zimmermann, et al. Ph.D.**

Interaction between rs3800373 and baseline adverse events on incident MDE

**rs3800373**

- CC: n=72
- CA: n=305
- AA: n=504

Interaction sign. (p<0.05) with adjustment for age, gender, any anxiety, SUD and correction for multiple testing

**Interaction**: CA vs. CC: ns

**Interaction**: AA vs. CC: ns

**Interaction**: CA vs. CC: p<1.0x10^-8

**Interaction**: AA vs. CC: p=1.1x10^-7
Cumulative lifetime incidences of MDE by rs3800373 and lifetime severe trauma prior to baseline

1: CA+AA / without severe trauma (N=730)
2: CA+AA / with severe trauma (N=79)
3: CC / without severe trauma (N=61)
4: CC / with severe trauma (N=11)

4 vs. 1:
HR=4.4*; 95%CI=1.9-10.1

4 vs. 2:
HR=3.8*; 95%CI=1.4-9.7

4 vs. 3:
HR=5.3*; 95%CI=1.8-15.6

* p < 0.05; Hazard ratios (HR) controlled for age, gender, anxiety and substance use disorders
DESIRABLES
Desirables

• Larger studies (much!)
• Replication
• Replication
• Replication
• Even better handle on over-fitting
• Longitudinal studies
• [Stronger effects]
The glass is half full.
The glass is half empty.
The glass has been downsized.
The glass has made a lateral move.